A Dissertation on

A CLINICAL STUDY OF RETINOBLASTOMA

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CERTIFICATE

This is to certify that **Dr.L.Subha,** Post Graduate student in M.S Ophthalmology, at Regional Institute of Ophthalmology and Government Ophthalmic hospital attached to Madras Medical College, Chennai, carried out this dissertation on "**A CLINICAL STUDY OF RETINOBLASTOMA"** under our direct guidance and supervision during the period from **May 2005 to March 2008**.

This dissertation is submitted to the TamilNadu Dr. MGR Medical University, Chennai for the fulfillment of award of M.S. Degree in Ophthalmology.

Prof. Dr. K. NAMITHA BHUVANESWARI,
Unit chief, Paediatric Ophthalmology Clinic,
RIO - GOH,
Chennai - 8

Prof. Dr. V. VELAYUTHAM,
Director & Superintendent,
RIO - GOH,
Chennai

Prof.Dr.T.P. KALANITI, M.D
Dean,
Madras Medical College,Chennai.

DECLARATION

I, **Dr.L.Subha,** solemnly declare that the dissertation titled **"A CLINICAL STUDY OF RETINOBLASTOMA"** has been prepared by me. This is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of M.S. Ophthalmology, degree Examination to be held in March 2008.

Place: Chennai

Date:

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CONTENTS

INTRODUCTION

Retinoblastoma is the most common intraocular malignancy of childhood [1] with an incidence of approximately 1 in 14,000 to 34,000 live births per year. Retinoblastoma accounts for 3% of all childhood malignancies in developed countries [2]. In developing countries such as India, retinoblastoma is usually the most frequent solid tumor seen in pediatric oncology units, suggesting that it might be more frequent in developing countries. In this setting, retinoblastoma is diagnosed late, usually when extraocular dissemination has occurred and the prognosis is poor. Late referral might account for the delayed diagnosis and treatment [3].

The survival rate of children with retinoblastoma has markedly improved over the past several decades in developed countries, but it still varies in developing countries. The 5-year survival rate is reported to be 95% and 87% respectively, in Europe and the United States [4]. Few estimates of survival rates of retinoblastoma have been reported from the Asia region. In Malaysia and Taiwan the 5 year survival rates vary from 55-80.9% for unilateral cases and no patients with bilateral disease survive beyond 5 years [5]. However, data regarding five year survival rates in India is scant. In this background, this study was undertaken to evaluate the salient clinical and epidemiological features of retinoblastoma.

HISTORICAL ASPECTS

Retinoblastoma was described first by **Peter Pawius** from Amsterdam in 1597. In 1809, **James Wardrop** referred to the tumor as fungus hematodes. During the early years the disease was called by terms such as ‘soft cancer’. The precise origin of the tumor from the retina was a matter of dispute for several years. It was thought to arise from the inner nuclear layer, the nerve fibre layer, and the photoreceptors. **Von Graefe** called it a ‘retinal sarcoma’, **Rudolf Virchow** termed it ‘glioma of the retina’. H. Knapp (1868) and Hirschberg (1868-9) introduced the term ‘glioma exophytum’ and ‘glioma endophytum’. **Flexner (1891) and Wintersteiner** (1897) defined the natural history, histology of these tumors and their metastases. The term retinoblastoma was coined by **Verhoeff** (1922). Von Graefe pointed out the need to remove a long section of the optic nerve at the time of enucleation [6]. **Reese and Ellsworth** proposed a classification of retinoblastoma in 1958 [7].

CLINICAL FORMS AND BIOLOGY

The unique place of retinoblastoma in oncology is due to its very distinct pattern of inheritance and from the fact that the RB1 gene was the first human cancer gene to be cloned. Retinoblastoma results from malignant transformation of primitive retinal cells before final differentiation. Because these cells disappear within the first few years of life, the tumor is seldom seen after 3 years of age. The predisposing gene is at 13q14.

Retinoblastoma may be heritable or non-heritable. About 60% of all patients with retinoblastoma have a nonheritable form of the disease with a normal life expectancy if they are cured of eye tumor. The tumor is unilateral, the average age of diagnosis is about 24 months and the risk of other cancers is virtually indistinguishable from the normal population [8]. 85% of patients with unilateral retinoblastoma fall into this category. In contrast, the remaining 40% have a heritable cancer predisposition syndrome due to RB1 germ line mutation. The average age at diagnosis is younger than the non-heritable form (newborn to 12 months) and they are predisposed to a variety of cancers throughout life. About 85% develop bilateral, multiple eye tumors. 2-3% develop midline intracranial tumors that involve the pineal or suprasellar region and are referred to as pinealoma, primitive neuroectodermal tumor and trilateral retinoblastoma.

Hereditary retinoblastoma patients have an elevated risk of osteosarcomas, soft tissue sarcomas and other mesenchymal tumors through their teenage years, melanomas and brain tumors through middle age and epithelial malignancies such as

lung and bladder cancer into later life. The risk of second malignancies is much greater in the field of radiation. This predisposition is due to the fact that hereditary patients carry germ line RB1 mutations (i.e. one allele of the tumor suppressor gene RB1 has mutated in all body cells), When a further mutogenic event affects the second allele ("second hit"), the cells undergoes malignant transformation. This "two-hit theory" was first proposed by **Knudson i**n 1971 [9], thus suggesting that retinoblastoma gene functions in a recessive manner. The deleted gene was later mapped to chromosome 13q14.1 to q 14.3 [10]. This retinoblastoma locus, RB1 is mutated in all forms of retinoblastoma, suggesting that chromosome 13 q14 is the gene locus for this tumor. Cavenee and co-workers using restriction fragment length polymorphic DNA probes compared DNA from normal and tumor tissue and found that one copy of the region around RB gene was lost during tumorigenesis. This was termed as loss of heterozygosity (or reduction of homozygosity). The authors showed that this genetic alteration was due to mitotic non disjunction or mitotic recombination, where a partial loss of one of a pair of chromosomes is repaired at mitosis by the duplication and transfer of a portion of its homolog [11].

‘THE FIRST HIT’:

The RB gene has 27 exons spanning over 200 kilobases of DNA. Less than 10% of retinoblastoma patients have a constitutional chromosome 13 q abnormality (usually a deletion) [12]. Extensive deletions are associated with the 13 q syndrome, which also included growth and mental retardation, facial dysmorphism, microcephaly, skeletal abnormalities and genitourinary abnormalities. Chromosomal abnormalities are detected by karyotyping.

A majority of RB gene mutations are small alterations involving one or a few nucleotides. These can be detected only by single strand conformational polymorphisms [SSCP], denaturing gradient gel electrophoresis [DGGE], chemical cleavage mismatch detection and direct sequencing. The majority of these are frameshift and nonsense mutations, missense mutations, splicing mutations and mutations in noncoding regions that result in a truncated unstable protein product [13]. Germ line RB mutations can be detected by using truncated RB protein mutants.

Most of the new germline mutations are of paternal origin, suggesting that the gene responsible is more susceptible during spermatogenesis [14].

“ THE SECOND HIT”:

Mutation of the second RB allele is due to chromosomal aberrations, usually recognized as loss of heterozygosity (LOH) by polymorphism analysis [12]. These mutations occur at a much higher rate than the first germ line mutation (10^3 vs. 10^7) [15]. Hence it is more sensitive to environmental factors such as ionizing radiation, thus the increased risk of radiation induced malignant tumors in survivors of retinoblastoma.

The most common mechanism leading to LOH is mitotic recombination [50%], followed by non-disjunction with or without subsequent reduplication (~ 40%). After the second hit has occurred, retinoblastoma cells rapidly accumulate additional genetic damage. It is possible than an additional mutation (third hit), probably involving a gene of the apoptotic pathway is necessary for final retinal tumor formation.

LOW PENETRANCE RETINOBLASTOMA:

Penetrance:

The frequency that a heritable disease is manifest in the offspring of affected individuals.

Expressivity:

The variability of clinical manifestations in affected individuals.

Disease eye ratio:

The ratio of the number of eyes containing tumors to the number of mutation carriers in a family. It identifies low penetrance retinoblastoma families by taking into account both penetrance and expressivity [16]. In general, reduced penetrance and expressivity tend to segregate in the same families [17]. The overall penetrance rate of retinoblastoma is 80-90%, which includes both high-penetrance and low-penetrance families [17]. Most low penetrance families have disease-eye ratios of 1:5 or greater. Most low-penetrance retinoblastoma results from mutations at the RB gene locus that result in an Rb protein with reduced activity [16,18,19]. One of the most common low penetrance mutations is a missense alteration at codon 661 [16,20].

ROLE OF RETINOBLASTOMA PROTEIN:

The product of the RB1 gene is a 110-kd nuclear phosphoprotein that acts by binding and inhibiting several proteins with growth-stimulating activity pRB is a key substrate for G1 cyclin-cdk complexes, which phosphorylates target gene products required for transition of the cell through G1.

The active pRb is the unphosphorylated gene product, which binds to several cellular proteins, among which is transcription factor E2F, which activates transcription of genes whose products are required for entry into the S phase of the cell cycle. During progression through G1, pRB undergoes additional phosphorylation. The result is a hyperphosphorylated form that persists through the S1-G2 and M phases. pRB appears to function as a tumor suppressor at least in part by inhibiting cell cycle progression past G1-S restriction point. Once cells traverse this restriction point and enters S phase, they become irreversibly committed to cell division.

Thus pRB stands as the major gatekeeper to control this critical point in growth regulation. Lack of pRB or its inactivation removes the pRB constraint on cell cycle control and the consequence is deregulated cell proliferation.

OVERVIEW OF RETINOBLASTOMA

Retinoblastoma is usually diagnosed between birth and the first 5 years of life. The tumor starts initially as one or more white masses usually in the posterior pole of the eye. Light reflected by the tumor causes a “cat’s eye” reflection in the pupil or a yellow glow rather a red glow as in the normal eyes. When the tumor destroys central vision, the presenting sign may be strabismus.

Initial tumors grow rapidly in the retina; as they expand they develop malignant characteristics leading to vitreous and subretinal seeding. The expanding mass leads to retinal detachment, neovascular glaucoma and/or intraocular hemorrhage before it spreads beyond the eye. Untreated, most intraocular retinoblastomas will expand directly into the optic nerve, brain and orbit or spread via hematogenous dissemination to bone marrow, bone and other organs. Some tumors spontaneously involute leading to phthisis.

EPIDEMIOLOGY OF RETINOBLASTOMA

Retinoblastoma is the most frequent neoplasm of the eye in childhood and accounts for 3% of all pediatric cancers. The average incidence is one in 14-18,00 live cancers. There is no sex or racial predilection. The human retina is not terminally differentiated till 3 years of age. It is during this period, in which primitive photoreceptor cells are stimulated to differentiate into the mature retina , that cells are at high risk of sustaining oncogenic events that result in the development of a neoplasm.

In developing regions of the world including Southern Asia, retinoblastoma is one of the single most common solid tumors of childhood; while in North America it is the sixth most common solid childhood tumor. The varied incidence is due to the varied incidence of unilateral non-heritable disease.

The incidence of heritable retinoblastoma among the various populations of the world is remarkably constant, providing strong evidence that environmental influences play little role in the etiology of the hereditary form of this tumor [21].

In marked contrast to the uniform incidence of heritable retinoblastoma worldwide, there are striking geographical differences in the indicence of non-heritable, unilateral form of retinoblastoma. The increased incidence of non-heritable retinoblastoma in the tropical regions may possibly be due to a viral etiology [Human Papilloma Virus] [22], though convincing evidence is not available. Another theory

proposed for the increased incidence of non-heritable retinoblastoma is that pregnant mothers in these countries eat a diet deficient in fruits and vegetables [22], leading to dietary deficiencies during pregnancy. Advanced paternal age is unequivocally associated with new sporadic germline mutations and sporadic heritable retinoblastoma [23].

PATHOGENESIS

Since all cells in a retinoblastoma tumor focus are identical, a new tumor cell will expand symmetrically as a round or hemispherical lesion that is homogenous. Because tumor growth begins in a single retinoblast cell, all intraocular retinoblastomas are initially confined to the retina.

Avascularity severely restricts the growth potential of tumors. Hence for the tumor to expand further, tumor angiogenesis is essential. Angiogenesis can be demonstrated by measuring 'relative tumor vascular density [RTVD]'. RTVD can be demonstrated by CD34 staining for vascular endothelium in specially stained histopathology sections. The RTVD is statistically greater in ocular tumors of patients with metastatic disease [24].

Another important property in tumor progress is loss of cellular adhesion or loss of anchorage. Retinoblastoma cells undergo vitreous or subretinal seeding when mutations in the tumor suppressor gene PTEN allow them to grow without extracellular matrix anchorage dependence. Tumor cells that invade adjacent tissue spaces enter into different, low oxygen, low nutrient microenvironment. The final end result is large avascular vitreous and subretinal masses. Further tumor growth leads to total retinal destruction, vitreous or subretinal hemorrhage, angle closure glaucoma due to pressure of the tumor pushing the iris lens diaphragm forward or from direct occlusion of the chamber angle by tumor cells or red blood cells or anterior chamber angle neovascularization. Tumor cells may invade the optic nerve and grow into the

chiasma and brain. Less commonly, they penetrate the sclera and expand as an orbital mass lesion. Since the ability to metastasize requires many mutations that enable the tumor cell to penetrate vessel wall layers, survive in the extravascular environment and develop new vessels to survive; metastasis implies prolonged presence of viable tumor cells.

The function and structure of the eye ensure that retinoblastomas are diagnosed and treated before they metastasize. Hence metastatic disease presents very rarely at initial diagnosis at least in developed countries.

CLASSIFICATION OF INTRAOCULAR RETINOBLASTOMA

The Reese-Ellsworth classification published originally in 1964, specifically predicts the likelihood of ocular salvage following treatment with external beam radiotherapy. The introduction of systemic chemotherapy in the 1980s led to the near abandonment of its use in most oncology centers. A new international classification system based on the natural history of retinoblastoma and on the likelihood of salvaging the eye when systemic chemotherapy is used as the primary treatment was developed.

REESE-ELLSWORTH CLASSIFICATION

This is a group classification system which deals only with organ-confined intraocular disease. In this system, eyes are divided into five groups on the basis of size, location and number of lesions and the presence of vitreous seeding [Table-1] [7].

Table 1 : Reese – Ellsworth Grouping of Suitability for Management of Retinoblastoma by Radiation Therapy.

STAGE	DESCRIPTION
Group I. Very Favorable	
I a	Solitary tumor smaller than 4 dd at or behind the equator
I b	Multiple tumors, none larger than 4 dd, all at or behind equator
Group II. Favorable	
II a	Solitary tumor 4-10 dd, at or behind equator
II b	Multiple tumors 4-10 dd, at or behind equator
Group III. Doubtful	
III a	Any lesion anterior to the equator
III b	Solitary tumor larger than 10 dd behind equator
Group IV. Unfavorable	
IV a	Multiple tumors, some larger than 10 dd
IV b	Any lesion extending anteriorly to the ora serrata
Group V. Very unfavorable	
V a	Massive tumors involving more than half the retina
V b	Vitreous seeding
Dd , disk diameter (1.5 mm)	

THE INTERNATIONAL CLASSIFICATION SYSTEM

Table 2 : International classification of intraocular retinoblastoma [25]

Group A – Very low risk • All tumors are 3 mm or smaller in greatest dimension, confined to the retina. • All tumors are located further than 3mm from the foveola and 1.5 mm from the optic disc
Group B – Low risk All remaining discrete retinal tumors without seeding • All tumors confined to the retina not in group A • Any tumor size and location with no vitreous or subretinal seeding
Group C- Moderate risk Discrete local disease with minimal focal subretinal or vitreous seeding • Tumors must be discrete • Subretinal fluid, present or past, without gross seeding, involving up to one quadrant of the retina • Local subretinal seeding, present or past, less than 5 mm from the tumor Focal fine vitreous seeding close to discrete tumor
Group D – High risk Diffuse disease with significant vitreous and/or vitreous seeding • Tumor(s) may be massive or diffuse • Subretinal fluid, present or past, up to total retinal detachment • Diffuse subretinal seeding, may include subretinal plaques or tumor nodules • Diffuse or massive vitreous disease may include ‘greasy’ seeds or avascular tumor masses

Group E – Very high risk

Presence of any one or more of these prognosis features

- Tumor touching the lens
- Neovascular glaucoma
- Tumor anterior to anterior vitreous face involving ciliary body or anterior segment
- Diffuse infiltrating retinoblastoma
- Opaque media from hemorrhage
- Tumor necrosis with aseptic orbital cellulitis
- Phthisis bulbi

This is based on the natural history of retinoblastoma and on the likelihood of salvaging the eye when systemic chemotherapy is used as the primary treatment. The risk of loss of the eye due to the tumor is graduated form ‘very low’ for Group A to ‘very high’ for Group E. In this system the morbidity of treatment increases from Group A to Group E.

ST. JUDE’S CLASSIFICATION

For patients undergoing enucleation, St. Jude Staging system is used which is a pathologic staging that incorporates other features known to influence modality of treatment and prognosis, such as choroidal involvement, optic nerve extension and presence of metastatic disease [26].

PATHOLOGY

Retinoblastoma arises from the photoreceptor elements of the inner layer of the retina, usually extending into the vitreous cavity as a fleshy nodular mass (endophytic retinoblastoma). Less frequently, it extends externally, causing secondary retinal detachment; in this case there is no localized visible vitreous nodule (exophytic retinoblastoma).

Macroscopically, retinoblastoma is soft and friable, and it tends to outgrow its blood supply, the result is necrosis and calcification. Because of friability of the tumor, dissemination within the vitreous and retina in the form of small white nodules (seeds) is common. In these cases, it may be difficult to differentiate multicentric primary tumor from disseminated tumor.

The microscopic appearance depends on the degree of differentiation. Undifferentiated retinoblastoma is composed of small, round, densely packed cells with hypochromatic nuclei and scant cytoplasm.

Homer Wright rosettes are composed of irregular circlets of tumor cells arranged around a tangle of fibrils with no lumen or internal limiting membrane.

Flexner-Wintersteiner rosettes- a cluster of low columnar cells arranged around a central lumen bounded by an eosinophilic membrane are specific for retinoblastoma;

seen in 70% of tumors.

Fleurettes are less common. If rosettes are present, the cells exhibit more ultrastructural characteristics of photoreceptor differentiation. Especially well-differentiated tumors composed almost entirely of fleurettes have been called retinoma or retinocytoma.

CLINICAL FEATURES OF RETINOBLASTOMA

In a retrospective review of 1265 patients with retinoblastoma over a period of 30 years – the most comprehensive study of retinoblastoma patients done so far, leucocoria was the presenting sign in 56.2% of the cases [28].Leucocoria is uniformly the most common presenting sign of retinoblastoma in most studies done in both the developing and the developed world [Table 3]. In a study done in Congolese children with retinoblastoma, 49% presented with Leucocoria [30]. In a study of 141 cases of retinoblastoma done in Turkey, retinoblastoma was the presenting sign in 82% of cases [31]. Tumors must occupy a large volume of the globe before they produce leucocoria that is visible to an unaided observer. Leucocoria correlates with the presence of advanced (RE group Va or Vb) disease.

Table 3 : Presenting signs of retinoblastoma in various studies

	New York [28] **(n=900)**	**Finland** [32] **(n=136)**	**United Kingdom** [33] **(n=139)**	**Switzerland** [34] **(n=50)**	**Philadelphia** [35] **(n=87)**	**AIIMS** [29] **(n=392)**
Leukocoria	56	54	32	62	55	72.2
Strabismus	20	18	20	20	21	10
Red eye	7	15	5	2	-	-
Amblyopia	5	8	-	6	-	-
Routine exam	3	1	9	2	4	1.5
Orbital cellulites	3	-	-	2	-	0.5
Anisocoria	2	4	-	2	4	-
Hetero-Chromia	1	1	-	2	2	-
Hyphema	1	-	1	-	1	0.25
‘Strange expression’	0.5	-	-	-	-	-
Nystagmus	0.5	-	-	-	-	-
White iris nodule	0.5	-	-	-	-	-
Anorexia	0.5	-	-	-	-	-
Associated signs	-	-	7	-	-	-
Unspecified	-	-	26	-	-	Proptosis : 13

The likelihood of observing leucocoria relates directly to the diameter of the pupil at the time of observation. Since the leucocoria is seen in dim light when the pupil dilates naturally, parents or family members often question their own observation. This will be reinforced if the pediatrician or primary care physician does not dilate the pupil and assures the family that there is no abnormality. Strabismus is the second most common sign and usually correlates with macular involvement [28]. Hence strabismus in the first six months of life always requires an immediate retinal examination to rule out retinoblastoma. Small tumors in the foveola or near the foveola can significantly reduce the visual acuity in that eye. Very advanced tumors can become painful as a result of secondary glaucoma.

The various presenting features of retinoblastoma as seen in various studies have been summarized in Table 3.

FACTORS LEADING TO DELAY IN DIAGNOSIS OF RETINOBLASTOMA:

The American Academy of Pediatrics policy statement says that: 1] All infants should have a red reflex test by age two months in a darkened room. 2] For the test to be considered normal the examiner must see symmetrical reflections in the two pupils. 3] If the examiner's efforts to see the red reflex are not successful, the examiner should either dilate the pupil before performing the test for a second time or immediately refer the child to an ophthalmologist [36].

A study done in the UK showed that nearly one quarter of patients were referred to an ophthalmologist only after 8 weeks of presentation. There was a significantly increased risk of diagnostic delay in younger patients, those presenting with squint rather than leucocoria, and those first presenting to a health visitor rather than a general practitioner. The risk of tumor invasion was significantly increased by diagnostic delay.

Hence primary health care professionals require education about the importance of ocular symptoms, especially squint, in pediatric patients [37]. Similarly, **Erwenne and Franco** reported that the risk of extraocular disease was strongly dependent on age at diagnosis and lateness of referral [3]. **DerKinderen** et al reported that early diagnosis in bilateral retinoblastoma improved survival and visual outcome [38]. In developing countries presentation with advanced disease is common and outcome is often dismal [39]. In a study done in Buenos Aires late diagnosis was due to parental delays and failure of the pediatrician to recognize the condition [40]. In

Argentina the survival rate for extraocular disease is only 36%, and all patients with central nervous system disease or distant metastases died [41].

PSEUDORETINOBLASTOMA:

In 500 consecutive referrals for retinoblastoma, simulating lesions were found in 212 of the 500 patients [42]. The three most common causes were: persistent hyperplastic vitreous (28%), Coat's disease (16%0 and presumed ocular Toxocariasis (16%). Other conditions that simulate retinoblastoma include congenital cataract, retinopathy of prematurity and congenital retinal folds. Solid intraocular tumors appear hyperintense on T1 weighted MRI images and showed contrast enhancement and hypointense on T2 weighted images, whereas secondary serous or exudative retinal detachment from intraocular lesions showed hyperintensity on both T1 and T2 weighted images and no contrast enhancement [43].

EVALUATION

Anesthesia and a maximally dilated pupil and scleral indentation are required to examine the entire retina. Initial evaluation should include assessment of visual acuity and an indirect ophthalmoscopic examination of the eyes. Retinoblastoma usually appears as a mass projecting into the vitreous, although the presence of retinal detachment or vitreous hemorrhage can make visualization difficult. A slit lamp examination of anterior or posterior vitreous to look for vitreous seeding should be done. Tonometric measurement of intraocular pressure in all cases; measurement of corneal diameter and an ultrasonic measurement of eye length are helpful in suspected glaucoma

IMAGING:

Additional imaging studies that aid in the diagnosis include B scan ultrasound, CT and MRI. B scan demonstrates intralesional calcium and helps in measuring tumor size. It can detect a tumor as small as 2 mm in diameter [44]. It is as good as CT in demonstrating presence of calcium in intraocular tumors. Ultrasound alone may lead to errors in diagnosis in cases of atypical retinoblastoma [no necrosis/calcification]. Hence CT scan is necessary in cases where calcium cannot be demonstrated by a B scan. MRI of the brain and orbits (with gadolinium contrast and fat suppression) helps to evaluate extraocular extension and optic nerve invasion and helps to diagnose ‘trilateral retinoblastoma’. Other causes of leucocoria can also be differentiated. MRI can demonstrate infiltrative spread to the Optic Nerve,

subarachnoid seeding and involvement of the brain. Both CT and MRI help in determining the extent of recurrent disease, extraocular spread and defining second primary tumor [45].

A fluorescein angiogram is useful in confirming the presence of neovascularization of the iris in cases of retinoblastoma with glaucoma and/or chronic retinal detachment. It also helps in differentiating active lesions (staining and dye accumulation) from inactive ones. It also helps in diagnosing a retinoma. Orbital films are of no value and should not be part of the workup. Fine needle aspiration should be done only in exceptional cases in which a diagnosis cannot be arrived at by any other means. Specular microscopy of the corneal endothelium may be useful in differentiating retinoblastoma cells (dark and light band reflections) from keratic precipitates on corneal endothelial surface (bright reflections with a peripheral dark rim) [46].

METASTATIC WORKUP:

Metastatic disease occurs in approximately 10-15% of patients, usually in

association with distinct intraocular features, such as deep choroidal and scleral invasion, or involvement of the iris-ciliary body and optic nerve beyond the lamina cribrosa. Metastatic workup should be performed in these patients and whenever there is clear evidence of tumor outside the eye. Studies should include bone marrow aspiration and biopsy from multiple sites, a bone scan and lumbar puncture (to search for tumor cells in the CSF). These studies are also recommended for patients receiving chemotherapy or radiation therapy before enucleation, as proper histologic evaluation cannot be performed.

TREATMENT OF RETINOBLASTOMA

PRINCIPLES OF TREATMENT:

Management of retinoblastoma is aimed at saving life and preserving useful vision and thus it must be individualized. Factors to be considered in treatment include unilaterality or bilaterality of disease, potential for vision, and staging.

SURGERY:

Enucleation is indicated for large tumors filling the vitreous for which there is little or no likelihood of restoring vision and in cases of tumor present in the anterior chamber or in association with neovascular glaucoma. For optimal staging, a long section (10-15mm) of Optic Nerve has to be removed with the globe.

FOCAL THERAPY:

Focal treatments are used for small tumors (<3-6mm), usually in patients with bilateral disease, and in combination with chemoreduction. Photocoagulation with argon laser is used to manage tumors situated at or posterior to the equator and to manage retinal neovascularization due to radiation therapy. Cryotherapy is used to manage small intraretinal tumors confined to the sensory retina without seeding [Shields JA].

An important focal method is transpupillary thermotherapy, in which focused heat is applied at sub coagulation levels. Combination of thermotherapy with chemotherapy has a synergistic effect. Hence thermo chemotherapy is becoming a

very important component in the management of intraocular retinoblastoma. In general, local control rates of 70-80% can be achieved.

RADIATION THERAPY:

Due to increasing use of chemoreduction in conjunction with intensive focal therapy, external beam megavoltage radiation therapy usually is reserved for cases in which other measures have failed, usually because of progression of vitreous and subretinal seeding and for tumors adjacent to the optic nerve. Because most patients undergoing radiation therapy have multifocal disease, the entire retinal surface has been irradiated to a uniform dose. The recommended total dose is 40-60 cGy in 180-200 cGy fractions. Many techniques can be used usually through lateral fields.

Three types of tumor regression have been categorized:

Type 1: Tumor shrinkage with calcium deposition; ‘cottage-cheese pattern’.

Type 2: Tumor is a grey homogenous mass characterized by partial shrinkage and loss of pink color of capillary injection. An annulus of atrophic pigment at the base of tumor is present.

Type 3: The mass has evidence of shrinkage, has lost pink color and has a nidus of calcium.

Radiation alone can cure 75-80% of patients. Addition of cyrotherapy or photocoagulation can improve results to 90%.

Radioactive plaque technique is used in the management of localized tumors. Indications include; solitary tumors with a diameter between 6-15 mm, tumor thickness of 10 mm or less and location of lesion greater than 3 mm from optic disc or fovea. I^{135} is the most widely used. A control rate of 85-90% can be achieved.

CHEMOTHERAPY:

Indications:

- Extraocular disease,
- Intraocular disease with high risk histologic features,
- Bilateral disease [in conjunction with aggressive focal therapy].

Agents include platinum compounds, cyclophosphamide, doxorubicin and vincristine .Chemotherapy can be given for two cycles followed by specific focal treatment after two months.

Adding local LASER hyperthermia to systemic carboplatin therapy enhances the binding of platinum to the DNA.

UNILATERAL RETINOBLASTOMA:

Since they have advanced tumors [RE IV-V] when they seek treatment, enucleation is the treatment of choice being 80% curative. Patients with high risk features on histology [deep choroidal invasion, involvement of anterior chamber, iris, ciliary body or retrolaminar optic nerve] need adjuvant therapy .Those with extraocular and metastatic disease need high dose chemotherapy, hematopoietic stem cell rescue, radiation therapy to orbit and other areas of bulky disease.

BILATERAL RETINOBLASTOMA:

Since bilateral retinoblastoma is multiple, develop at an earlier age and patients are at risk of development of extraocular tumors throughout life, chemoreduction followed by aggressive focal therapy has replaced enucleation and EBT. The use of systemic chemotherapy for cytoreduction, coupled with intensive sequential focal therapy [cryotherapy, laser, photocoagulation, thermotherapy and brachytherapy] has resulted in increased eye salvage rates and a decrease in the use of radiation therapy. The best results are achieved with a combination of vincristine, carboplatin, etoposide. Salvage rates for RE I-III approaches 100% when these techniques are used. For RE IV-V, rates are not better than 50-70% and EBT is usually needed. Intraocular concentrations are 7-10 times higher when carboplatins are administered subconjunctivally.

PROGNOSIS:

Factors affecting survival include: High risk histologic features, delay in diagnosis and multiple episodes of recurrent disease in an eye.

Risk among offspring of survivors of retinoblastoma: The risk of retinoblastoma arising in offspring of bilateral [hereditary disease] is 45%. The risk is 2.5% in cases of offspring of unilateral retinoblastoma.

Risk among siblings: In the presence of family history, siblings of patients with bilateral tumors have a 45% risk while siblings of patients with unilateral tumors have a 30% risk. In absence of family history, siblings of patients with bilateral tumors have a 2% risk, while those with unilateral tumors have a 1% risk

AIMS AND OBJECTIVES

The aims of this study were to analyze;

- Age incidence
- Modes of presentation
- Time lag between onset of symptoms and presentation
- Staging
- Reasons for delay in presentation
- Correlation between delay in diagnosis and staging
- Radiological features
- Management and follow-up of cases which were diagnosed as retinoblastoma.

MATERIALS AND METHODS

This study was a prospective study conducted at the Regional Institute of Ophthalmology, Govt. Ophthalmic Hospital from May 2005 to September 2007. All the children suspected to have retinoblastoma and cases which were referred from other hospitals were subjected to detailed clinical examination. 26 consecutive patients [31 eyes] with retinoblastoma admitted from May 2005 to March 2008 were included in the study. Detailed clinical history was obtained with regard to the nature of the disease like appearance of “amaurotic cats’ eye”, watering, pain, redness, protrusion of the eyeballs, squint, hyphaema, hypopyon, defective vision etc. The exact duration, progress and the eye or eyes involved was also noted.

In the family history details regarding the consanguinity between the parents and about the health and affection of the siblings and other relatives were noted. The family was also interviewed to determine if they had taken the child to a pediatrician or an ophthalmologist after noticing the first clinical abnormality. A record of the time between the onset of symptoms and diagnosis was made. Socioeconomic information was obtained from the family at diagnosis.

General examination included examination of other systems to rule out distant metastasis. Ocular examination included the following: vision, pupillary reaction,

detailed fundus examination both direct and indirect under general anesthesia after total mydriasis with atropinisation. Ocular tension was recorded under General Anesthesia by Perkin's hand-held applanation tonometer. Investigation included haematological examination pertaining to the disease and special investigations like CT scan orbit and brain, USG B scan, serum and aqueous LDH levels. In those cases where enucleation was done, the excised eye and the cut end of the optic nerve was subjected to histopathological examination. Those cases which needed radiotherapy was referred to Radiology Department, GH and chemotherapy to medical Oncology Department, GH. All those patients were asked to come for follow-up. Careful examination of the empty socket and the apparently normal eye was done in the follow up at frequent intervals.

OBSERVATION AND DISCUSSION

In the present study a total number of 26 cases of established retinoblastoma were examined for the following:

Table 1: Age at presentation

Age at presentation	No. of cases	Percentage
< 1 yr	4	15.38
1 – 3 yr	14	53.84
> 3 yr	8	30.76

Table 2: Family History

Family history	No. of cases			Mean age at presentation
	< 1 yr	1-3 yr	> 3 yr	
Present(5)	3	2	0	15.2 months
Absent(21)	1	12	8	34.14 months

Of the 26 cases examined, the age of onset of 53.8% cases was between 1-3 years and the age of onset of 15.38% cases were below 1 year and 30.76% above 3 years of age. The youngest child with RB in this study was 90 days old male with unilateral involvement. Majority of those patients with a family history of retinoblastoma presented with RB before the age of 1 year. Our findings were similar to those of **Abramson DH et** al (96.5% patients presenting with a family history did so before the age of 24 months) [28]. Studies done in India show a similar age trend. A study done by **Shanmugam MP** et al shows the mean age at presentation of Retinoblastoma was 23.98+/-23.37 months [48].

Table 3: Sex incidence

Sex	No. of cases	Percentage
Males	10	38.46
Females	16	61.84

In our study, there were 10(38.96%) males and 16(61.54%) females. Male: Female ratio was 0.62. Studies by **Khandekar R** (29 cases) [49], **Mukhopadyaya S** et al [50] (study of 23 cases) showed that females were more affected similar to our study. However, other studies by **Alegria V** et al [51], **Kaimbo et al** [30] have shown that the gender ratio Male: Female > 1.

Table 4: Laterality

Laterality	No. of cases	Percentage
Unilateral		
Right eye	11	42.30
Left eye	10	38.46
Bilateral	5	19.23

Table 5 : Mean age at presentation according to laterality:

Laterality	No. of cases			Mean age at presentation
	< 1 yr	1-3 yr	> 3 yr	
Bilateral	3	2	0	15.2 months
Unilateral	1	12	8	34.14 months

Retinoblastoma involved one eye in 21 cases, 80.7% cases and both eyes in 5(19.23%) cases. For unilateral cases, the mean age at presentation was 2.58 years and for bilateral it was 15.2 months. Studies by Kaimbo et al and Watts showed that the unilateral cases presented at a mean age of 36 months and bilateral cases had a

mean age at presentation of 12 months [30].

Table 6: Presenting sign

Presenting sign	No. of cases	Percentage
Leucocoria	22	70.96
Orbital cellulitis	3	9.67
Anterior Staphyloma	1	3.22
Hyphaema	1	3.22
Leucocoria with Strabismus	1	3.22
Nystagmus with Leucocoria	2	6.45
Leucocoria with proptosis	1	3.22

Leucocoria was the commonest presentation in our study accounting for 67.74% of cases. Similar observations have been made in other studies done in New York, Philadelphia, Finland, Switzerland [32-35]. Leucocoria was the most common presenting sign in more than 50% of patients with retinoblastoma in all these studies. The percentage of patients who presented with orbital cellulitis was 9.67%; this high incidence has not been seen in other studies [New York (3%), Switzerland (2%)]. This can be explained by the delay in diagnosis and referral to an ophthalmologist by the primary care physicians and ignorance among the parents.

None of the retinoblastoma patients in our study were detected on routine pediatric examination. Hence it is necessary that all infants should have a red reflex test done by during routine visits to the pediatrician in the very early stage. Strabismus was a presenting sign in only 3.22% of our patients in contrast to other studies which report a higher incidence.

Table 7: Intraocular Tension (by Perkin's Tonometry)

Tension [mm Hg]	No. of cases	Percentage
10-20	3	11.11
20-30	10	37.03
30-40	10	37.03
40-50	4	14.81

About 88.89 % of patients had raised intraocular tension [> 20 mm Hg]. Raised intraocular tension is a major differentiating feature of retinoblastoma from other causes of Leucocoria. IOP was not recorded in 3 cases of orbital cellulitis and one case of anterior staphyloma.

Table 8: Calcification in ultrasound and CT

Calcification	Ultrasound		CT	
	Eyes	%	Eyes	%
Present	27	87.09	31	100
Absent	4	12.90	0	0

Calcification was not detected by B scan Ultrasonography in 12.90% of cases. CT demonstrated calcification in all 31 eyes studied. Hence CT scan should be done in cases where calcium cannot be demonstrated by a B scan. [44].

Table 9: Staging (International Classification)

Stage	No. of cases	Percentage
A	0	0
B	0	0
C	11	35.48
D	11	35.48
E	9	29.03

Most cases presented during the late stages of disease, hence the visual outcome in almost all our cases was poor. Studies in developing countries have shown that presentation with advanced disease is common and outcome is often dismal [39]. The reasons for presentation with advanced stage disease are delays in referral and parental delay in seeking treatment.

Table 10: Time interval between onset of symptoms and visit to an ophthalmologist

First symptom	Median lag time in weeks
Leukocoria	4 weeks(1 week – 52 weeks)
Orbital cellulitis	10 weeks (4 week – 1 4 weeks)
Others	2 weeks(1 week – 12 weeks)

Patients with orbital cellulitis had a greater time lag between onset of symptoms and referral to an ophthalmologist, while those with leukocoria had a lesser time lag. Since orbital cellulitis is a rare initial presenting sign of retinoblastoma there was a greater time lag between onset of disease and presentation to an ophthalmologist. The overall median time lag was 5 weeks(range 1-52 weeks) for all types of presenting signs.

Table 11: Mode of treatment

Mode of treatment	No. of cases	Percentage
Enucleation	17	54.83
Enucleation followed by EBRT and chemo	3	9.67
EBRT + chemotherapy	9	29.03
Exenteration	1	3.22
Refused Treatment	1	3.22

Majority of our patients (64.5%) underwent enucleation. Enucleation was followed by EBRT and chemotherapy (9.67%) in cases which showed optic nerve involvement on histopathological examination.

EBRT and Chemotherapy (29.03%) was the mode of treatment for cases which had demonstrable intracranial metastasis and bony involvement. One eye with Leucocoria and proptosis was found to have orbital invasion and hence underwent exenteration.

In bilateral cases, the extensively diseased eye was enucleated and the less involved eye received EBRT and chemotherapy.

Table 12: Follow up of cases

Outcome	No. of cases	Percentage
Deaths	3	11.53
Recurrence in orbital socket	3	11.53
No recurrence (till study period)	13	50
Lost to follow-up	7	26.92

All cases were followed monthly during the initial six months following their discharge from our institution, and then 3 monthly thereafter. Three cases of retinoblastoma died during the study period due to systemic metastases. These patients had undergone EBRT and chemotherapy for treatment of systemic disease. Recurrence of tumor in the empty socket was seen in 3 cases which received further cycles of EBRT. Recurrence of tumor was not demonstrated in 13 cases during the study period. These cases had undergone enucleation alone and histopathology showed no optic nerve involvement. 7 cases were lost to follow-up.

RESULTS AND CONCLUSION

A total of 26 retinoblastoma patients and 31 eyes were studied over a three year period for age at presentation, laterality, family history of retinoblastoma, presenting signs, time lag between symptom onset and presentation. All the patients underwent detailed evaluation for disease staging. The treatment that these patients had was recorded.

1. It was found that the mean age of presentation for patients with a positive family history was 15.2 months, while those with no family history of retinoblastoma presented at a later mean age of 34.14 months.

2. For unilateral cases (21 cases had unilateral disease), the mean age at presentation was 2.58 years while those with bilateral disease had a mean age at presentation of 15.2 months.

3. The commonest presenting sign was leukocoria (67.74%). A significant percentage of patients (9.67%) presented with orbital cellulitis.

4. Ultrasonography demonstrated intraocular calcification in 89.65% of patients whereas CT scan demonstrated calcification in all the patients. Hence all patients with suspected retinoblastoma should undergo a CT scan to detect

calcification.

5. 68.4% of patients presented with high and very high risk disease [Stage D and E] as per International Classification System of staging, making vision salvage extremely difficult.

6. There was a overall median lag time of 5 weeks (range 1-52 weeks) between onset of symptoms and presentation to our center. The median lag time was greater (10 weeks) in those who presented with orbital cellulitis.

7. 64.5% the patients with retinoblastoma underwent enucleation. About one-third underwent treatment for orbital extension and disseminated disease.

8. Our study shows that patients with retinoblastoma seek treatment in the later stages of disease due to delay in presentation and delay in referral. Early referral and timely presentation to the ophthalmologist is necessary if vision salvage is to be a reality.

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LIST OF SURGERIES

S. No	NAME	AG/SX	IP NO	DIAGNOSIS	D. O. S	PROCEDURE
1.	GOPAL	65/M	382619	RE – IMC	10.07.05	RE-ECCE/PCIOL
2.	PARVATHI	58/F	382759	BE–IMCL>R	17.07.05	RE-ECCE/PCIOL
3.	KAMSALA	50/F	382947	BE–IMCL>R	31.07.05	LE-ECCE/PCIOL
4.	SULOCHANA	60/F	390756	BE–IMCR>L	27.04.06	RE-ECCE/PCIOL
5.	BABU	53/M	391787	BE-IMC R>L	10.05.06	RE-ECCE/PCIOL
6.	KRISHNAVENI	70/F	393782	RE – MC	12.07.06	RE-ECCE/PCIOL
7.	SAVITHRI	58/F	390999	BE–IMC R>L	18.08.06	RE-ECCE/PCIOL
8.	SUSAI	59/M	396179	LE – IMC	03.10.06	LE-ECCE/PCIOL
9.	ANANDAN	65/M	399979	RE – IMC	08.11.06	RE-ECCE/PCIOL
10.	NARAYANAN	70/M	392147	LE – IMC	25.01.07	LE – SICS/PCIOL
11.	VELUSAMY	52/M	392436	BE–IMC L>R	01.02.07	RE – SICS/PCIOL
12.	MUNIAMMAL	65/F	399423	BE-IMC L>R	15.02.07	LE – SICS/PCIOL
13.	RANI	52/F	399415	LE – MC	17.02.07	LE – SICS/PCIOL
14.	ASHRAFUNISA	68/F	399442	BE-IMC R>L	22.02.07	RE – SICS/PCIOL
15.	AYISHA BEE	55/F	399961	BE-IMC R>L	09.03.07	RE – SICS/PCIOL
16.	SUNDARAMMA	65/F	400200	RE – MC	16.03.07	RE – SICS/PCIOL
17.	SAMSHUDIN	58/M	400474	RE – IMC	23.03.07	RE – SICS/PCIOL
18.	INDRANI	52/F	400576	RE – IMC	30.03.07	RE – SICS/PCIOL
19.	MUNIAMMAL	60/F	394493	RE-FUNGAL CORNEAL ULCER WITH HYPOPYON	22.06.07	RE-TKP 9MM OVER 8MM
20.	RAVI	17/M	25789	LE CHALAZION	21.05.06	LE – I & C
21.	KAVERI	37/F	27240	RE-PTERYGIUM	21.05.06	EXCISION
22.	RAJAMMAL	35/F	384392	LE-FUNGAL CORNEAL ULCER WITH HYPOPYON	20.06.06	LE – AC WASH WITH AMP – B
23.	MUNIAPPAN	59/M	83120	LE-PAN OPHTHALMITIS	26.11.06	LE-EVISCERATIONQ

24.	SHANTHI	52/F	376292	RE-ABSOLUTE GLAUCOMA	08.12.06	RE-CYCLOCRYO
25.	LAKSHMI	50/F	396830	RE-CHR. DACROCYSTITIS	07.02.07	RE DCT
26.	BABU	09/M	396857	RE-TRAUMATIC ENDOPHTHALMITIS	07.02.07	RE-INTRA VITREAL INJ. OF BR.SP.ANTBIOTICS
27.	MALAKONDIAH	55/M	387906	BE-SEC ACG		RECOMBINED SUR
28.	GIRIJA	45/F	402574	BE-PACG		RE-AG SURGERY
29.	SHANKAR	32/M	402574	RE-CHR. DACROCYSTITIS	08.05.07	RE – DCR
30.	JAIBUNISA	15/F	397265	RE-OLD RHEG.RD	16.06.07	RE-RD SURG (360º ENCIRCLAGE WITH CRYO WITH SRF DRAINAGE)